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EXAMINER	
MYERS, CARLA J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,741	FOEKENS ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,17,19-24,45,57-59,61,62,67 and 77* is/are pending in the application.

4a) Of the above claim(s) *19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,17,20-24,45,57-59,61,62,67 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/2/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, the PITX2 gene, and SEQ ID NO: 83 in the reply filed on May 20, 2008 is acknowledged. The traversal is on the ground(s) that SEQ ID NO: 83 and 135 constitute preferred regions of the PITX2 gene and thereby it would not require undue burden to search these sequences together. This is not found persuasive because SEQ ID NO: 83 and 135 constitute distinct regions of the PITX2 gene that differ with respect to their nucleotide sequence and their methylation pattern. A search for methods which analyze the methylation pattern of SEQ ID NO: 83 in order to predict a patient's response to treatment would not be co-extensive with a search for methods which analyze the methylation pattern of SEQ ID NO: 135 in order to predict a patient's response to treatment. Further, a finding that methods which analyze the methylation pattern of SEQ ID NO: 83 in order to predict a patient's response to treatment are novel or unobvious over the prior art would not necessarily extend to a finding that methods which analyze the methylation pattern of SEQ ID NO: 135 in order to predict a patient's response to treatment were also novel or unobvious over the prior art. Similarly, a finding that methods which analyze the methylation pattern of SEQ ID NO: 83 in order to predict a patient's response to treatment are anticipated or obvious over the prior art would not necessarily extend to a finding that methods which analyze the methylation pattern of SEQ ID NO: 135 in order to predict a patient's response to treatment are also anticipated or obvious over the prior art. Accordingly, it is maintained

that undue burden would be required to examine the sequences of SEQ ID NO: 83 together with SEQ ID NO: 135 (and SEQ ID NO :516, 517, 789 and 790).

The requirement is still deemed proper and is therefore made FINAL.

However, Applicant's arguments regarding the rejoinder of SEQ ID NO: 83 with SEQ ID NO: 411, 412, 685 and 686 are persuasive. Accordingly, each of SEQ ID NO: 83, 411, 412, 685 and 686 has been examined herein.

2. Claims 1, 17, 19, 20-24, 45, 57-59, 61, 62, 67 and 77 are pending.

Claim 19 is withdrawn from consideration as being directed to a non-elected invention.

With respect to claims 45, 57-59, 61 and 77, the subject matter of SEQ ID NO: 135, 411, 412, 685 and 686 has been withdrawn from consideration, as being directed to a non-elected invention.

With respect to claims 62, 67 and 77, the subject matter of SEQ ID NO: 135 has been withdrawn from consideration, as being drawn to a non-elected invention.

Specification

3. The specification is objected to because it does not contain, as a separate section, a section entitled brief description of the drawings, as required by 37 CFR 1.74. This objection may be overcome by adding the title "Brief Description of the Drawings" to page 32 prior to the final paragraph.

4. The specification is objected to because at pages 34-35, Figures 6, 8, 10 and 12 are described in terms of containing "red" and "green" elements. In particular, the specification states that "Figures 6, 8, 10 and 12 are the red-green versions of the

preceding figures (i.e. figures 5, 7, 9 and 11 respectively). Red indicates total methylation at a given CpG position, green represents no methylation at the particular position." However, these figures are in black and white (i.e., no color drawings have been filed). Accordingly, the description of the Figures is not consistent with the Figures themselves.

Claim Rejections - 35 USC § 112 second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20, 45, 57-59, 61, 62, 67 and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is indefinite over the recitation of "said cell proliferative disorder of the breast tissue" because this phrase lacks proper antecedent basis. This rejection may be overcome by amendment of the claim to recite "said breast tissue cell proliferative disorder" in place of "said cell proliferative disorder of the breast tissue."

Claims 45, 57-59, 61 and 77 are indefinite over the recitation of "the nucleic acid amplificate" because this phrase lacks proper antecedent basis. While the claims recite a step of amplifying a pretreated DNA sequence, the claims do not specifically recite a step of producing a nucleic acid amplificate. Thereby, it is unclear as to what constitutes "the nucleic acid amplificate."

Claims 62, 66 and 67 are indefinite over the recitation of "the DNA digest" because this phrase lacks proper antecedent basis. While the claims recite a step of

digesting genomic DNA and determining the DNA fragments generated or not generated, the claims do not previously recite a step that results in a DNA digest. It is thereby unclear as to what constitutes the DNA digest and what is intended to be the relationship between the DNA digest and the DNA fragments.

Claim Rejections - 35 USC § 112 - Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 17, 20-24, 45, 57-59, 61, 62, 67 and 77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to methods for screening for predicting responsiveness of a subject with a breast tissue proliferative disorder to a therapy comprising determining

the genomic methylation status of at least one CpG dinucleotide in the PITX2 gene to thereby predict responsiveness of the subject to a therapy.

The claims are inclusive of methods which predict the responsiveness of any subject to therapy, and thereby include predicting the responsiveness of rats, dogs, horses, pigs, pandas etc to therapy.

The claims encompass methods in which the therapy is any type of therapy with a drug that targets any component of the estrogen receptor pathway or drugs that are involved in estrogen metabolism, production or secretion. The drug may be an adjuvant treatment or a primary therapy. Thereby, the claims encompass determining responsiveness to a very wide range of drugs (antisense drugs, ribozymes, antibody therapy, organic and inorganic compounds), which differ in their structure and mechanism of action.

The claims further include methods in which the drug is used to treat any breast tissue proliferative disorder, and thereby encompass a significantly broad genus of disorders, including benign and malignant disorders and specifically including ductal carcinoma in situ, lobular carcinoma, colloid carcinoma, tubular carcinoma, medullary carcinoma, metaplastic carcinoma, intraductal carcinoma in situ, lobular carcinoma in situ and papillary carcinoma in situ (claim 20). These disorders differ with respect to their symptoms and etiology.

The claims also include methods in which any biological sample from a subject is analyzed for CpG methylation in a PITX2 gene. The claims thereby include the analysis of methylation of CpGs of the PITX2 gene obtained from any frozen tissue or paraffin

embedded tissue from any organ in the subject, any acellular sample containing PITX2 nucleic acids (e.g., plasma or serum), or any other biological sample, such as ductal lavage fluid, nipple aspiration fluid, urine, feces, tears or saliva. The claims also specifically include analyzing cell lines generated from a subject (see claim 77).

The claims include analyzing any sequence in the PITX2 gene for the methylation status of one or more CpG dinucleotides. The PITX2 gene comprises 25,584 bases and thereby is expected to include numerous CpG dinucleotides. While claims 17, 45, 57-59, 61, 62, 67 and 77 include analyzing a PITX2 gene sequence comprising the 6343 nucleotides of SEQ ID NO: 83, 411, 412, 685 or 686, these claims also recite the analysis of any complementary sequence or contiguous portions thereof. Thereby, the claims include analyzing any CpG dinucleotide in any PITX2 sequences (coding regions, introns, 5' and 3' untranslated regions) that share any level of complementarity (20%, 10% etc) with any portion of SEQ ID NO: 83, 411, 412, 685 or 686.

Moreover, the claims broadly recite determining the genomic DNA methylation status "wherein predicting responsiveness of the subject to the therapy is afforded." The claims do not set forth how the results of determining the DNA methylation status are used to predict responsiveness. Thereby, the claims encompass predicting responsiveness based on either the presence or absence of methylation at any one or more CpG dinucleotides or based on either hypermethylation or hypomethylation of any one or more CpG dinucleotides.

Nature of the Invention

The claims encompass predicting responsiveness to therapy for a breast tissue proliferative disorder by assaying for the methylation status of a CpG dinucleotide in the PITX2 gene. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification (page 11) teaches that "The gene PITX-2 (NM_.000325) encodes a transcription factor (PITX-2) which is known to be expressed during development of anterior structures such as the eye, teeth, and anterior pituitary. Although the expression of this gene is associated with cell differentiation and proliferation it has no heretofore recognized role in carcinogenesis or responsiveness to endocrine treatment."

In Example 1 (page 40), the specification teaches methylation analysis of genes from 200 patients, including the PITX2 gene. The sequence of the primers and the gene sequence analyzed are set forth in Tables 1 and 2. Regarding the elected invention, the specification teaches amplification of a 408 bp region of the 6343bp sequence of SEQ ID NO: 83 using the primers of SEQ ID NO: 1055 and 1056 (page 54). Microarray analysis was performed to determine the CpG methylation status of the amplification products. The specification does not clearly set forth the source of the nucleic acids that were analyzed. The data obtained from Example 1 (dataset 1) is presented in Figures 5 to 12. These figures are characterized on page 34 as showing the methylation status of two classes of tissues, although the source of the tissue is not provided. Also,

while page 40 of the specification states that 200 patients were analyzed, page 40 does not characterize the patients in terms of their type of disease (i.e., type of breast tissue cell proliferative disorder), type of treatment, age, gender etc. In characterizing Figure 1, the specification (page 32) indicates that the figure shows the model of endocrine treatment of stage 1-3 breast cancer wherein primary treatment was surgery followed by adjuvant therapy with Tamoxifen. With respect to Figure 1, responders are characterized as "remaining below the limit of detectability for the duration of the observation" and non-responders are characterized as having a period of disease free survival followed by relapse when the carcinoma reached a level of detectability (pages 32-33). However, the specification does not teach whether this information applies to all examples provided in the specification. Therefore, with respect to the examples provided in the specification, the information regarding the characterization of the subjects (type, stage etc of the disorder), drug used for treatment, and criteria for defining responders versus non-responders is unclear.

For a "Data set 1", responders or non-responders to Tamoxifen as an adjuvant surgery following surgery were analyzed. The source of the tissues analyzed is not stated (e.g., breast, skin, cell lines, blood). Figures 5 and 6 list a p value for PITX2 as 0.995. Page 34 characterizes this figure as showing p values which are the probabilities that the observed distribution occurred by chance. This information appears to indicate that PITX2 CpG methylation was not associated with response or lack of response to tamoxifen adjuvant therapy following surgery. The figures are also characterized as showing the positions of specific CpGs in the gene, and as showing degrees of

methylation with light colors representing low levels of methylation and dark colors representing high levels of methylation. However, the figures do not identify the particular nucleotide position of the CpGs within the PITX2 gene or the amplified fragment of the PITX2 gene. Thereby, it cannot be ascertained which particular CpGs show a difference in methylation status between responders and non-responders.

The specification at pages 44-45 discusses the results associated with a "Data set 2: Adjuvant setting." It is stated that every CpG was put into a Cox proportional hazard model with predictive factors of N-stage and tumor size. The specification states that the best marker was the PITX2 gene. However, the specification fails to state what PITX2 is a marker of. For example, is PITX2 the "best marker" of survival, N-stage, tumor size, response to treatment? It is also stated that oligonucleotide 3522:2087 gives information about survival time independent of nStage. However, the specification does not characterize the identily of this oligonucleotide. Also, in this example, the number of patients analyzed is not provided, nor are the patients characterized with respect to their disorder, treatment, age, sex etc. Moreover, survival time, N-stage and tumor size are considered to be prognostic factors and are not equivalent to determining the responsiveness to therapy.

At page 45, the specification discusses a "Data set 4: Metastatic setting." While the subjects are characterized as being treated with tamoxifen, the subjects are not characterized with respect to their disorder. It is stated that individual CpGs measured were combined for each gene. However, the region of the PITX2 gene analyzed, and thereby the CpGs analyzed is not clearly stated. Figure 16 is characterized as showing

the best 11 amplificates of the data obtained in Dataset 4. The PITX2 gene is not included as one of the 11 best amplificates.

At page 46, the specification discusses a "Data set 4: Adjuvant setting." It is stated that the results are provided in figures 17-21 as Kaplan-Meier estimated disease-free survival curves. PITX2 is said to have a p value of p = 3e-04. The results for PITX2 are provided in Figure 19. The number of subjects analyzed is listed as 278. However, the subjects are not clearly characterized with respect to their disorder or as to whether N is the number of each of the responder and non-responder subjects or N is the combined number of responder. Also, the X and Y axis of this figure are not characterized. It appears that the figure intends to compare the proportion of subjects that are responders or non-responders with disease-free survival over the period (months?) recited in the X axis. The specification (page 46) states that "the mean methylation over all oligo-pairs for that amplificate was calculated and the population split into equal sized groups according to their mean methylation values." While figure 19 compares responders to non-responders, the figure does not distinguish between their methylation status (hypermethylation versus hypomethylation). Thereby, it is unclear as to whether an increase in methylation was considered to be associated with responders or non-responders. Also, the specification does not clearly characterize the identity of the PITX2 amplification products that were analyzed.

Regarding Data set 3, the specification (page 46) teaches that methylation of several genes were associated with response to tamoxifen and include STMNI, SFN, S100A2, SYK, GRIN2D, PSA, COX7A2L,VTN, and PRKCD. PITX2 is not included in

this list. At page 48, the specification concludes that: "we have shown for the first time that an epigenetic profile based on the CpG island DNA methylation status of promoter regions of just five genes can predict the likelihood of therapy response in patients with ER-positive advanced breast cancer treated with tamoxifen therapy." The 5 "independent predicting genes" are listed on page 67 as PSA-t, STMN1, GRIN2d, TGFBR2 and S100A2. PITX2 is not included in this list.

Accordingly, the information provided in the specification is not sufficiently complete or detailed to allow one to interpret the information. Complete information is not provided in the examples regarding each of the type of disorder present in the subjects, the source of the sample analyzed (primary breast tissue or other types of primary tissue, cell lines, blood etc), the age, sex, gender and number of subjects analyzed, the type of treatment (primary or adjuvant), drug(s) used for therapy, and the criteria used to define responsiveness to therapy. Also, the specification does not clearly characterize any CpGs or particular CpG methylation patterns in the PITX2 gene which are associated with an increase or decrease in methylation and whose methylation status is correlated with response to treatment. Accordingly, insufficient information is provided in the specification to allow the skilled artisan to predictably extrapolate the results obtained therein to the response to any treatment of any subject with any breast tissue cell proliferative disorder.

The Predictability or Unpredictability of the Art :

The art of determining an association between methylation status and response to therapy is highly unpredictable. While methylation status is known to effect gene

expression, there is no clear art recognized association between methylation status and response to any therapy for any breast tissue cell proliferative disorder.

The unpredictability of predicting responsiveness to therapy by assaying for PITX2 methylation at any CpG dinucleotide is highlighted by the teachings in the following post-filing date art, of which the present inventors are co-authors.

In particular, Martens et al (Cancer Research. 2005. 65(10): 4101-4107) teaches the results of a study of the methylation status of 117 genes, including the PITX2 gene, in 200 steroid hormone receptor responsive tumors in patients who received tamoxifen as first-line treatment for recurrent breast cancer. Martens did not observe an association between methylation status of PITX2 (see Supplemental Tables 1 and 2).

The findings of Martens were discussed by Nimmrich et al (Breast Cancer Research and Treatment. 2008. 111:429-437). With respect to the Martens reference, Nimmrich states that "earlier work from our group in clinical specimens did not find *PITX2* DNA-methylation to be associated with intrinsic tamoxifen resistance in metastatic breast cancer" (page 430). At page 434, Nimmrich states that in the previous retrospective study of Martens, "we did not find DNA-methylation of PITX2 of the primary tumor to be associated with tamoxifen response (given as a first-line single endocrine agent) in metastatic breast cancer. Nimmrich studied DNA-methylation of the PITX2 gene in untreated lymph node-negative hormone receptor positive breast cancer patients. The authors found that hypermethylation of PITX2 was associated with a poor prognosis and disease progression in these patients. Nimmrich also clarifies the distinction between a marker that is prognostic and markers that are predictive of

response to treatment, stating that "a prognostic factor is not necessarily also a predictive marker, or vice versa" (page 434). Nimmrich also acknowledges that differences in methylation results may occur between early stage and advanced breast cancer due to the differences in tumor biology (page 434). The teachings of Nimmrich support the unpredictability of extrapolating the results obtained with one type of breast tissue proliferative disorder to other types of breast tissue proliferative disorders (e.g., early stage breast cancer as compared to late stage, metastatic breast cancer), and with one type of therapy to other types of therapy (e.g., primary treatment with tamoxifen as compared to adjuvant treatment of recurrent cancer with tamoxifen).

The claims further encompass methods in which any sample type is analyzed for the methylation status of CpGs. Thereby, the claims encompass analyzing such diverse samples as serum/plasma, urine, brain tissue, saliva etc. However, it has not been established that changes in methylation status in subjects having proliferation diseases occur in all tissues and cells and in acellular nucleic acids. The fact that gene expression may vary significantly between tissue types, and thereby methylation patterns may also vary between tissue types, is well accepted in the art. However, no information is provided in the specification regarding the methylation pattern of the PITX2 gene in blood samples, spinal cord, lymphatic fluid, urine, feces, or tears etc from patients having a breast tissue proliferative disorder. Also, no information is provided regarding the level of methylation of extracellular PITX2 nucleic acids in biological fluids, such as serum or plasma. In the absence of evidence showing a change in methylation status in a representative number of diverse sample types, it is highly unpredictable as

to whether the results obtained in one sample type, such as primary breast tissue, can be extrapolated to other tissue types.

It is also highly unpredictable as to whether cell lines generated from patient samples can be analyzed as predictive of response to therapy (as is specifically encompassed by claim 77). It is well accepted that the genetic alterations which occur in cell lines are not necessarily reflective of the genetic changes which occur *in vivo*. For instance, Dermer, G.B. (Bio/Technology (1994) 12: 320) states that "The cell lines in which cancer is usually studied are unsuitable for the job. They do not mimic conditions in the human body." Dermer concludes that "Petri dish cancer is really a poor representation of malignancy, with characteristics profoundly different from the human disease." Since the results obtained in vitro in cell lines cannot be extrapolated to in vivo, knowledge that a gene is methylated or not methylated in a cell line does not allow one to conclude that this gene is associated with response to treatment *in vivo*.

Further, the present claims are inclusive of methods in which response to treatment is predicted in any human or non-human subject. However, the art of extrapolating expression profiling results from one animal to other animals is highly unpredictable. There is no information provided in the specification which indicate that methylation status of PITX2 nucleic acids in humans are the same as those present in non-human organisms, such as mice, dogs, goats, horses etc.

As stated on page 11 of the specifciation, the function of the PITX2 gene in the occurrence of cancer is currently unknown. As recently as 2008, Nimmrich states that "(f)rom a biological point of view, the role of PITX2 DNA-methylation and cancer is

unknown" (page 435, col. 1). The lack of a clear structure – function relationship between PITX2 methylation and cancer, and particular response to treatment of cancer with drugs that target the estrogen receptor, further compounds the unpredictability of extrapolating results obtained from humans to other organisms. In view of the variability in gene expression levels and thereby expected variability in methylation patterns between organisms and the lack of a structure-function relationship between methylation of the PITX2 gene and response to treatment, insufficient information is provided in the specification to establish that any results obtained in the specification regarding PITX2 methylation in humans can be extrapolated to a representative number of diverse non-human organisms.

It is further unpredictable as to whether any single CpG or any combination of any CpGs in any region of the PITX2 gene can be analyzed for the methylation status as indicative of response to treatment. The claims do not require any type of comparison step with a control, non-cancer or non-responsive sample, and thereby include methods in which the presence or absence of methylation at a single CpG is detected as predictive of response. However, the specification has not established such an association between any single CpG and response to any treatment. Further, the results in the specification appear to be limited to a 408bp region amplified using the primers of SEQ ID NO: 1056 and 1055 (page 54). It is well known in the art that different regions of a gene may be methylated in cancer tissues and in normal tissues. Thereby, the occurrence of any one methylated CpG alone is not necessarily predictive of response to treatment. Further, the effect of methylation may vary depending on the

location of the methylated CpG. For example, methylation of CpGs present in the promoter region of a gene may alter gene expression, whereas methylation of CpGs in coding sequences of a gene may not effect gene expression. The unpredictability of applying methylation results to the prediction of a phenotype is supported by the teachings of Ushijima (Nature Reviews. 2005. 5: 223-231). Ushijima teaches that "interpretation of differential methylation has proven difficult because the significance of methylation alterations depends on the genomic region, and functions of the CpG islands at specific sites have not been fully clarified" (see abstract). Ushijima teaches that both hypermethylation and hypomethylation are associated with the occurrence of cancer (page 223). Ushijima (page 223) also teaches that "it has become recognized that methylation in cancer cells frequently occurs in CGIs outside promoter regions, which do not repress gene transcription, and also in promoter CGIs of genes that cannot be regarded as tumour-suppressor genes. Even in normal cells, methylation of specific CGIs frequently occurs. Therefore, to identify novel tumour suppressor genes silenced in cancer cells by CGI methylation it is necessary to carefully select the particular CGIs to be included in the analysis."

Quantity of Experimentation and Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably identify additional animals whose PITX2 methylation status is correlated with response to treatment. The specification does not teach the existence of homologues of PITX2 nucleic acids in a representative number of non-human organisms. There is

also no information provided regarding the functional activity of PITX2 nucleic acids in cancer which would allow one to conclude that PITX2 nucleic acids have a similar functional role in contributing to the response to ER-directed therapies in a representative number of non-human organisms.

Additionally, there is no specific guidance provided in the specification as to the types of cells or tissues, other than primary breast tissue, which one would be expected to show a change in methylation status in subjects having breast cancer. One cannot determine a priori which tissues or biological fluids will contain PITX2 nucleic acids showing an altered methylation pattern as predictive of response to therapy. Such information can only be obtained through experimentation.

The specification does not provide sufficient guidance as to how to determine which particular CpGs in the PITX2 gene are to be analyzed as predictive of response to therapy. The claims encompass methods in which any single CpG or any combination of CpGs in any coding or non-coding region of the PITX2 gene are analyzed for their methylation status to thereby "afford" prediction of responsiveness to therapy. The claims also include analyzing a 6343 bp region of the PITX2 gene recited in SEQ ID NO: 83, or any sequence comprising a portion of SEQ ID NO: 83 or any sequence having any level of complementarity thereto (e.g., 20% or 10% complementarity). However, it appears that the specification analyzed a region consisting of only 408 nucleotides of SEQ ID NO: 83. While Figures 5 and 6 are characterized as illustrating the CpGs in the PITX2 gene that have an increased or decreased level of methylation, these figures do not clearly identify the location of

particular CpGs or combinations of CpGs that should be analyzed in order to predict response to therapy. It is also unclear as to whether an increase in methylation (relative to a control, non-cancer sample?) is associated with response to therapy or is associated with a lack of response to therapy. Thereby, insufficient guidance is provided in the specification as to how to interpret the results obtained from determining the methylation status of any one or more CpGs in any portion of the PITX2 gene to thereby predict responsiveness to therapy.

Extensive experimentation would be required to identify additional organisms and tissues in which PITX2 methylation is correlated with response to treatment with a drug that targets an estrogen receptor pathway, estrogen metabolism, production or secretion. While methods for determining CpG methylation status are known in the art, such methods provide only the general guidelines that allow researchers to randomly determine if particular CpGs or regions of a gene containing CpGs are methylated. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional organisms and tissues/fluids and particular CpGs in which an altered CpG methylation status will be correlated with response to therapy that targets estrogen receptors.

Working Examples

The specification does not specifically provide any working examples in which response of a patient having a breast cancer cell proliferative disorder to therapy is predicted by assaying for the methylation status of any one or more CpG dinucleotides.

The specification does not provide any working examples of methods in which response to therapy is predicted in non-human subjects.

The specification does not provide any working examples in which response to therapy is predicted by assaying cell lines, blood samples, urine samples, plasma samples, etc for the methylation status of CpG dinucleotides.

The specification does not provide any working examples in which response to any non-tamoxifen therapy is predicted wherein the drug is one that targets any component of the estrogen receptor pathway or one that is involved in estrogen metabolism, production or secretion.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the present application, the specification does not provide sufficient information regarding the study population in order to allow one to extrapolate the findings obtained therein to the general population. As discussed above, the examples set forth in the specification do not clearly characterize each study group with respect to the type of disorder of the subjects studied, the type of therapy employed, whether the therapy was primary or adjuvant, the criteria for defining a responder versus a non-responder, the CpG dinucleotides or combination of dinucleotides which showed a change in methylation status, whether the change in methylation status was an increase or decrease in methylation, and the type of sample that was analyzed. Moreover, the teachings in the specification and post-filing date art appear to indicate that while the PITX2 gene may be a prognostic factor, the methylation status of PITX2 is not predictive of response to therapy.

Further, if it can be established that the data in the specification shows that methylation status of PITX2 is correlated with response to treatment, the claims would not be considered to bear a reasonable correlation to the scope of enablement because the claims encompass predicting responsiveness to any therapy that targets an estrogen receptor pathway component in any subject having any breast tissue cell proliferative disorder by assaying for methylation of any one or more CpG dinucleotides in any coding region, intron region, or 5' or 3' untranslated region of the PITX2 gene. Further, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach a representative number of non-human organisms in which PITX2 methylation levels are modified as predictive of response to

therapy. Nor does the specification teach a change in PITX2 methylation status in a representative number of diverse tissue and fluid and acellular DNA samples encompassed by the claims. In view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 17-24, 45, 57-59, 61, 62, 67, and 77 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6-8, and 11-16 of copending Application No. 10/582,705. Although the conflicting claims are not identical, they are not patentably distinct from each other

because the present claims and the claims of '705 are both inclusive of methods of predicting the response of a subject having a cell proliferative disorder of the breast tissue to a treatment comprising determining the methylation status of one or more CpG positions within the PITX2 gene to thereby predict a subject's response to treatment. While the claims of '705 do not define the treatment as one that target the estrogen receptor pathway or that are involved in estrogen metabolism, production or secretion and particularly do not recite that the treatment is tamoxifen, when read in light of the specification of '705 it is cleared that the treatment is intended to specifically include treatments that target the estrogen receptor pathway and treatments that are involved in estrogen metabolism, production or secretion, and particularly include treatment with tamoxifen (see paras [0191], [0378] and [0476] of the PGPUB for '705, i.e., 20080254447). Further, while the claims of '705 do not specifically recite that the target sequence of the PITX2 gene comprises SEQ ID NO: 83, 411, 412, 685 or 686, the claims of '705 do include analyzing the methylation status of the target region of SEQ ID NO: 23. Since the present claims encompass methods that analyze a sequence having any level of complementarity to any contiguous portion (of any length) of SEQ ID NO: 83, 411, 412, 685 or 686, the present claims broadly encompass analyzing essentially any target region and thus encompass analyzing the same target region as claimed in '705.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/
Primary Examiner, Art Unit 1634